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Second line Antiretroviral Treatment failure and predictors among adults in northwest Ethiopia

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ACRONYMS

ABSTRACT

ABC	Abacavir
AHR	Adjusted hazard ratio
AIDS	Acquired Immunodeficiency Disease
ART	Antiretroviral Therapy
ATV/r	Atazanavir + ritonavir
AZT	Zidovudine
BMI	Body Mass Index
CI	Confidence Interval
CPT	Cotrimoxazole Prophylactic Therapy
ddI	Didanosine
d4T	Stavudine
EDHS	Ethopia demographic and health survey
EFV	Efavirenz
FMOH	Federal Ministry of Health
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
INH	Isoniazid
IQR	Inter Quartile Range
LTFU	Lost to Follow Up
LPV/r	Lopinavir/ritonavir
NNRTI	Non Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
PI	protease inhibitors
PLWHA	People living with HIV/AIDS
3TC	Lamivudine
TDF	Tenofovir
TO	Transfer out
UNAIDS	United Nations Programme on HIV/AIDS
WHO	World Health Organisation

Introduction: The rate of switch from first-line to second-line regimen and number patients taking second line ART is increasing from time to time, and in Ethiopia 1.5% HIV patients on ART are on second line regimen. Though some studies based in Ethiopia investigate the outcomes of first-line HIV treatment; to date, no study has been done regarding second line treatment. This study aims to anticipate the rate of second line regimens failure and predictors and thereby to inform respective stakeholders and assist in planning for the need of third line regimens in the future.

Objective: To assess second line Antiretroviral treatment failure and predictors among adults in northwest Ethiopia.

Methods: Institution based retrospective follow up study was conducted at University of Gondar, Flege Hiwot referral and Debretabor Hospitals from March 30, 2015 to May 18, 2015 among 356 clients in the age of 15 and above. The data were collected from patient charts, computer soft copies and registries. Life table was used to estimate the cumulative survival. Both bi-variable and multivariable Cox proportional hazards models were used to identify predictor of failure. 95% confidence level was used.

Result: Out 356 participants, 198 (55.62%) are males and mean age of patients at switch was 36.13 $\pm$ 8.9 years. Study subjects were followed for a minimum of 6 months and the median follow up period was 32.25 months (IQR=37.8 months).A total 67(18.82%) patients develop treatment failure. The incidence rate of failure was 61.7/1000 person year and the cumulative probabilities of survival at 12, 24, and 60, months were 0.94, 0.86, and 0.7654 respectively. Furthermore 62.7 % of failures were occurred within the first two year of follow up. Being in WHO clinical stage IV(AHR=2.6, 95%CI:1.3, 5.14), CD4 count <100 cells/mm^3 (AHR=1.78, 95%CI: 1.03, 3.076), age 50 and above(AHR=2.32, 95%CI: 1.016, 5.32) change in weight (AHR=0.916, 95%CI:0.88, 0.955), and switching in the calendar year September 2103 to October 2014(AHR=5.178454 , 95%CI: 1.16, 23.07)were significant and independent predictors of failure.

Conclusion and recommendations: The rate of treatment failure was comparable as compared to many sub-Saharan African studies and majority of failures were occurring in the first two years after switch. Hence close follow up of patients in the early period after switch and provision of an alternative third line regimen should be considered.

1. INTRODUCTION

1.1 statement of the problem

Human Immunodeficiency Virus (HIV) is a global challenge for the past three decades. Globally in 2013, 35 million were living with HIV (1)with an estimated 24.7 million people living with HIV in sub-Saharan Africa, nearly 71% of the global total(1, 2) and in Ethiopia the HIV prevalence among adults age 15-49 in the 2011 Ethiopia Demographic Health Survey(EDHS) is 1.5 percent (3) with an estimated incidence of 35,002 and death of 52,405 by 2014(4) (5).

Since 1995, Anti retroviral treatment (ART) saved the lives of millions globally and has substantially decreased morbidity and mortality in people living with HIV/AIDS (PLWHA) (6). Based on United Nations Program on HIV/AIDS (UNAIDS) report of 2014 globally as many as 13,950,296 people were accessing ART(2). For the 2013-14 year, the Federal Ministry of Health of Ethiopa(FMOH) reported that 1047 health facilities providing ART, 805,948 PLWHA who were ever enrolled in HIV/AIDS care, 492,649 PLWHA who had ever started ART, and 344,344 current ART users (7)and 1.5 % of these were on second line treatment. Amhara regional state comprises the highest number with 102,088 current ART users. In Ethiopia since the beginning of free ART,from 2005 to 2013, death duet to HIV/AIDS decreased by 63%(2).

Most patients begin treatment on a standard first-line regimen. The first-line treatment consists of a combination of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) with one non-nucleoside reverse transcriptase inhibitors (NNRTI); second-line treatment then utilizes two NRTIs not previously used in that particular patient for their first line treatment, with the addition of one protease inhibitors (PI) (8, 9). Treatment failure of this initial Highly Active Anti retroviral treatment (HAART) regimen is a common, though not inevitable, event(10) .

Second-line regimens are used when first-line drugs no longer protect the immune system, as measured by a patient's CD-4 cell count, HIV viral load, or clinical picture. Standard combinations do not work for everyone, particularly if they have contracted a

drug-resistant strain of the virus(11). Though first-line medications are frequently effective, viral mutation and drug resistance(12) do occur and are followed by treatment failure, which requires switching to a second-line regimen. However , many patients in sub-Saharan Africa remain on failing first-line regimens(13), and the rate of switch is increasing from time to time(14),(15).

According to different studies showed, switching patients to second-line regimens reduces mortality(14), increases viral suppression and improves immune reconstitution(16, 17) ,increases life expectancy (18) and decrease the spread of drug resistance (19). Although the magnitude of patients taking second line ART is small (20) due to delay in switching from first-line(21, 22) as well as challenges in drug availability and adherence, it needs a great attention.

However, some studies conducted in different sub Saharan countries, to our knowledge, no studies regarding second-line ART failure have been conducted in Ethiopia particularly in the study area. We proposed to measure the treatment failure and its predictors after shifts to second-line regimens, which is the last treatment option for those who have failed first-line treatment.

Therefore this study aims to anticipate the rate and predictors of second line regimen failure, to inform respective stakeholders and assist in planning for the challenge in HIV control strategy in the future.

1.2. Literature review

1.2.1 Treatment failure of second line ART

Once the patients who are living with HIV/AIDS are shifted from first line regimen to second line regimen, there are different fates that will be expected from the patient. As said before, after some follow up period a patient may die, LTFU, develop treatment failure, he or she may transferred to another facility or they might alive in care.

Different studies assessed treatment failure in different way with respect to clinical, Immunological and/or virological criteria According to an observational study done in Asia among those who used secondline ART for more than six months, the rates of treatment failure was 8.8 per 100 patient/years were (95% confidence interval: 7.1 to 10.9)(23). A to multi-centered study conducted in Asia and Africa, recorded failure of any type was 19% with an overall Incidence of 195 per 1000 person-years and 119 (18.8%) met World Health Organization failure criteria after a median 11.9 months following the start of second-line therapy, and at 1 and 2 years of second-line start,12% and 28% of patients, respectively, had recorded failure of any type(24). In another prospective follow up study conducted in six sub Saharan Africa countries to determine re-suppression of drug-resistant HIV-1 by second-line ART treatment failure was assessed by different approaches and , (13.9%) experienced virological failure, 12.1% of patients developed immunological failure and 6.3 percent experienced clinical failure(25).

A retrospective follow p study done in rural South Africa among patients switched due to virological failure from first line treatment, the rate of treatment failure was 25.1%, (26) and in the same setting with another study, treatment failure at 24 month was 25%(27)

According to a meta-analysis of different studies including adults and children who used secondline ART in developing countries, pooled treatment failure assessed by virological failure, was 21.79% at six months, 23.06% at 12 months, 26.65% at 24 months, and 38.02% at 36 months (28). Another observational cohort study done in

South Africa among second line ART users which assessed treatment failure by virological way revealed that, the rate of failure every six month at each point ranges from 3% to 16% and by the end of 12 month after switch it was 13%(29). A prospective follow up study conducted in Nigeria to assess viral mutation of second-line ART, by virological monitoring, treatment failure was 10% at the end of the study(30).

As shown by different studies done, death after switch has also a great contribution with a different range of rate. In Georgia, 10.7 percent (31) ,In another study conducted in sub-Saharan Africa, Asia and Latin America 8 percent of patients died after a median follow-up of 5 month(32, 33), in a study done in Zambia and Malawi with an incidence of 19.2 (15.2–23.9) per 1000 person-years (14) in another study involved eleven sub-Saharan African countries with a rate of 5.0 per 100 person-years(13).As well as lost to follow up(LTFU) is also an important fate with 16.16% in South Africa revealed (34), 7.8% in a cohort study done in Sub-Saharan Africa (25).

In managing patients who switched to second line ART, transfer out and patient retention has considerable implications. As per a study done in south Africa, retention in care was 74.04 percent (34). A study done in rural south Africa to assess second line ART outcome, retention rate at the end of follow-up whilst on second-line ART was 72.8% and 7.9% of them were transferred out(TO) (26). Additionally, According to a Prospective Cohort study on second-Line ART in Sub-Saharan Africa TO was 1.6%(25).

1.2.2 Predictors of second-line ART outcome

Multiple studies done in Asia and Africa have shown that age and sex are significant socio-demographic determinants in the occurrence failure among patients taking first line and second-line ART and especially among secondline users, being old was a significant predictor of failure (23, 35-37) as well as being male was also being male predicts failure particularly in first line users(35, 36, 38). According to different a study done in sub India, and a negative change in body weight also had a significant effect on treatment failure (39).

According to multi-centered study conducted in Asia and Africa, and also the same study done in south Africa, treatment failure rates increased with lower CD4 cell counts when second-line therapy was started(24, 29). According to studies done in China, South Africa, rural Southern Africa involving three countries among adult first line ART users, lower baseline CD4 cell count was also a major predictor of death(36, 38, 40).
In accordance with a retrospective follow up study of the evaluation of five-year outcomes of initial patients treated in Botswana's National ART Program and Other study conducted in rural Southern Africa among adult ART users, being at advanced clinical stage was a significant predictor of failure and death (25, 36, 41).Further more as presents in a systematic review and meta analysis on the outcome of second line ART in developing countries, as the duration of ART intake increases treatment failure rate also increases(28).
In a cohort study to compare the tenofovir (TDF) containing and non containing second-line ART in Zambia and South Africa; mortality was lower among patients taking TDF containing regimen as compared to those without TDF(42).In another cohort of patients in Asia and Africa, failure rates were lower in those who changed 2 nucleoside reverse transcriptase inhibitors (NRTIs) at the time of second line ART than those changed one NRTI(24). Prophylaxis for opportunitisic infection also affects loss to follow-up. In a cohort follow-up study done at Mizan-Aman General Hospital in Ethiopia, among patients on first-line ART who were not on isoniazid (INH) prophylaxis were at higher risk of loss to follow up (33). A two-year prospective follow up study in the Oromiya

Region showed that cotrimoxazole prophylaxis therapy (CPT) at or before ART initiation was associated also with lower mortality.(43)

Conceptual frame work

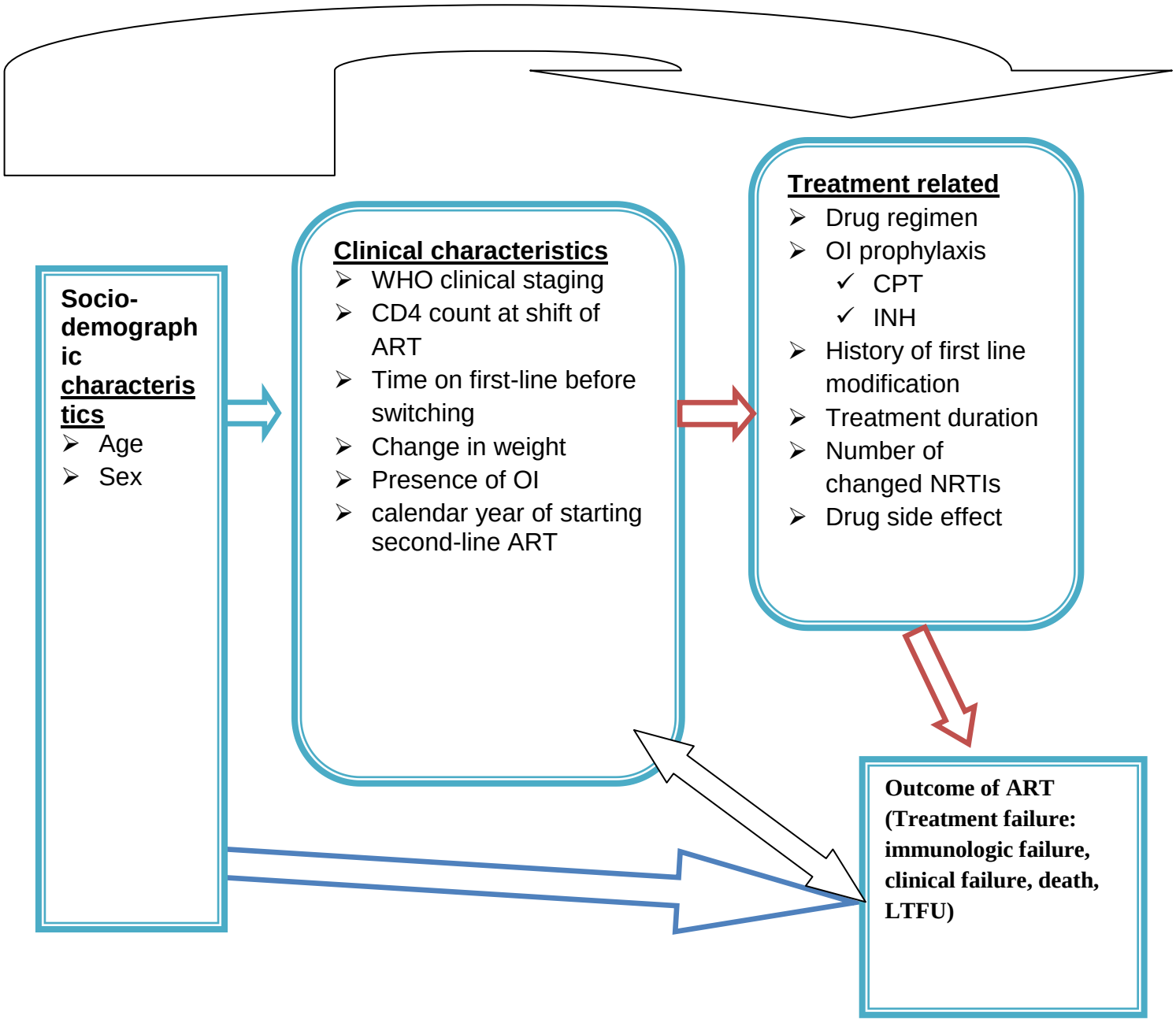

Figure1. Conceptual framework of secondline ART outcome

1.3 Justification of the study

Second-line HAART regimens are indicated for patients who are forced to discontinue their initial treatment regimen as a consequence of treatment failure, drug toxicity or poor adherence. However, their outcome is not yet studied specially in our country despite that living with HIV longer is one of the global strategies. Provision of ARV treatment by itself is not enough to control the problems of HIV treatment unless we monitor and evaluate its outcome through scientific research. Though some studies based in Ethiopia investigate the outcomes of first-line HIV treatment; no study, to our knowledge, has been done regarding second line treatment. Since second line treatments are the next and the only options as per to the Ethiopian ART treatment guideline, it is crucial and timely to know the rate of failure and determinant factors of second line treatment. This study will help to further evaluate the progress in Ethiopia's strategy against HIV/AIDS, to anticipate the effect of second-line regimens, to inform respective stakeholders about the current state of the uptake of second-line ART, and to assist in planning for the possible need of future, third line regimens.

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2. OBJECTIVE

2.1 General objective

- To determine second line Antiretroviral treatment failure and predictors among adults in northwest Ethiopia, 2015

2.2 Specific objective

- To determine second line Antiretroviral treatment failure among adults in northwest Ethiopia, 2015
- To identify predictors of second line Antiretroviral treatment failure among adults in northwest Ethiopia, 2015

3. METHODS

3.1 Study design

Institution based retrospective follow up study was conducted.

3.2 Study area and period

The study was conducted in University of Gondar Hospital, Felege Hiwot referral Hospital and Debre-tabor Hospital from March 30, 2015 to May 18, 2015. Patients who switched between september 2006 to October 2014 were included and followed until April 2015.

University of Gondar Referral Hospital HIV care clinic was one of the areas. It is located in North Gondar administrative zone, Amhara National Regional state, which is far from about 750 km Northwest of Addis Ababa (the capital city of Ethiopia). According to the 2007 population and housing census report, the total population size of Gondar town was estimated to be 206,987. Currently Gondar town has one Referral Hospital and five government Health Centers. University of Gondar Referral Hospital is a teaching Hospital which serves more than five million people of the North Gondar zone and peoples of the neighboring zones. The HIV care service of the Hospital was initiated in 2005 and has three clinics: Adult ART clinic, Pediatric ART clinic, and VCT clinic.

The second area was Felege Hiwot Referral Hospital which is located in Bahirdar town, Amhara National Regional State, Ethiopia. Bahirdar is the capital city of Amhara National Regional State and it is located 562 kms from Addis Ababa and 180 kms from Gondar. The hospital founded in 1963 and served for a catchment population of 5 to 7 million. Currently, apart from other services, Felege Hiwot Referral Hospital is providing HIV chronic care (both pre ART and ART) services for clients who attend chronic care and treatment services. The ART clinic has 6 outpatient rooms (OPD), one VCT, one pharmacy, one laboratory and one adherence counseling rooms. A total of 9 nurses, 3 general practitioners, 4 data clerks, 3 pharmacists and 15 adherence counselors are currently working. Since 2005 in which the hospital started ART, 16314 adults and 1383 pediatrics patients are enrolled. Currently 5401 adults are actively following their treatment.

The third study area was Debretabor Hospital which is located in Debretabor 665 kms from Addis Ababa. It serves for a catchment population of a round 2million. Currently, apart from other services, Debretabor Hospital is providing HIV chronic care (both pre ART and ART) services for clients who attend chronic care and treatment services. It has two OPDs, one pharmacy and one laboratory. Currently in the clinic, three nurses, two general practitioners, four adherence counselors and two data clerks are working.

3.3 Source and study population

The target population for this study includes all HIV positive adults age15 years and above who are taking second ling ART in northwest Ethiopia.

3.4 Inclusion and Exclusion Criteria

Inclusion Criteria

- All HIV positive adults (age >=15 years) on second line ART and switched from first line regimen and took second line ART for at least six months.

Exclusion criteria

- Patients who have less than two follow up CD4 count, transferred in after switch and who had incomplete baseline information were excluded.

3.5 Sample size and sampling procedures

In a prospective follow up study conducted in six sub Saharan Africa countries (Kenya, Nigeria, South Africa, Uganda, Zambia, and Zimbabwe) to determine re-suppression of Drug-Resistant HIV-1 by second-line ART after first-line failure, immunological failure was diagnosed in 12.1 percent, and 6.3 percent experienced clinical failure. Death due to HIV occurred in 4.5percent. 1.6 percent of subjects transferred out of the study and another 7.8 percent were lost to follow-up. Finally, a WHO clinical staging of 4 at the time of switch was a significant pedictor of failure with Hazards Ratio of 5.25 (25). Based on this similar literature, the sample size for this study is calculated as follows:

Outcome	proportion	Level of confidence	Margin of error	Final sample size
immunological failure	12.1%	95%	4%	255
clinical failure	6.3%	95%	3%	252
death	4.5%	95%	3%	183
lost to follow-up	7.8%	95%	**3%**	**307**
Predictors	**Assumptions**	**Proportions**	**Hazard ratio**	**Sample size**
WHO clinical stage 4(failure)	*Power=90%* *CI= 95%* *1:1 Ratio*	*P1= 31.8%* *P2 = 67.567%*	2.03	158

According to the sample size calculation, we used the largest of all which is **307** and since the number of patients in the three sites who fulfilled was **356**, we incorporated the remaining 49 cards to increase the power of the study. Out 356, 29 were from Debre tabor hospital, 151 from university of Gondar hospital and 176 from Felege Hiwot referral hospital.

3.6 Variables of the study

Dependent variable

Treatment failure of secondline ART and its time of occurrence

Explanatory variables

Socio-demographic characteristics: Age, sex

Clinical characteristics: WHO clinical staging, CD4 count at shift of ART, length of time on first-line ART, change in weight, presence of OI, calendar year of starting second-line ART

Treatment related: Drug regimen, OI prophylaxis, CPT, INH, history of first line modification, treatment duration, number of changed NRTIs, and drug side effect.

3.7 Operational definitions

Second-line regimens: is a boosted PI-based regimen, following a first-line regimen of one NNRTI and two NRTIs.

Censored: An individual followed second line ART for more than six months and still on follow-up or transferred out but not developed treatment failure.

Clinical failure: New or recurrent clinical event indicating severe immunodeficiency. WHO clinical stage 4 condition and certain WHO clinical stage 3 conditions (such as pulmonary TB and severe bacterial infections which may also indicate treatment failure) after 6 months of effective treatment.

Immunological failure: Failure is defined if at least one of the criteria below is fulfilled: follow up CD4 count fall to or below baseline values, a 50% fall from on treatment peak value, or persistent CD4 levels below 100 cells/mm^3.

Death: Death from any cause in a patient on second -line ART.

Transferred out - Those patients who are transferred to other health care facilities.

Transferred in - Those patients who are transferred from other facilities and accepted by the hospital.

Loss to follow up (LTFU): Is defined in a patient who is not receiving ARTs refill for a period of 3 months or longer from the last clinic attendance, and is not yet classified as ‘dead’ or ‘transferred-out’.

Treatment failure: was considered as a composite outcome of immunological failure, clinical failure, death and LTFU. If a patient had one of the four outcomes, he/she was

considered as having treatment failure. This is because as showed from different studies, the cause of majority of deaths is treatment failure, as well as most of patients who lost from follow up are those having treatment failure and majority them will died after being lost(13, 39, 44, 45).

3.8. Data collection procedures

Data collectors: A standardized data extraction check-list was prepared in English. Four health officers and 5 BSc nurses who have experience in working at ART clinic were participated in the data collection process after half day theoretical and half day practical training given. The data clerks and card room workers of the three hospital were also supported them by identifying the cards of patients.

Data collection procedure: Before going to collect data, the records to be reviewed (both baseline and follow-up records) were identified by their medical registration/card number. Then, together with the data clerk working at each respective ART clinic, data collectors reviewed and extracted data from patient charts and registries. For those cards which have incomplete information, the computer data base were used to supplement the information provided in the cards. Cards of patients switched from September 2006 up to October 2014 were included.

Data quality control

Training on the objective of the study and how to review the documents as per the data extraction format was given to data collectors and the supervisor for one day prior to data collection. The data extraction checklist was pre-tested for consistency of understanding the review tools and completeness of data items on 10 charts and the necessary adjustments were made on the final data extraction format. The Principal Investigator, with two other supervisors who are MPH candidate having clinical background and MSc candidate in Tropical infectious disease and HIV Medicine, supervised the overall process. The filled formats were checked for completeness by the Principal Investigator and/or the supervisors on daily basis.

3.9. Data processing and analysis

The data was entered in to EPI info version 7 and transferred to STATA version 12.0 for analysis. Descriptive and summary statistics was carried out. We observed rate of failure of the composite outcome (treatment failure) and each of the outcomes separately. Person time at risk was measured starting from the time of switch until each patient ends the follow up. Patients who switched from September 2006 up to October 2014 were included in the analysis. Life table was used to estimate the cumulative survival of patients and Log rank tests were used to compare survival curves between the different categories of the explanatory variables. Schoenfeld residuals test(both global and scaled) and -Ln(-ln) graph was used to check cox proportional hazard assumption. Both bivariate and multi variate Cox proportional hazards models were used to identify predictor variables. Variables having p value 0.2 or less in the bi-variable analysis were fitted in to the multi variable model. Ninety five percent confidence interval of hazard ratio (HR) was computed and variables having p - value less than 0.05 in the multi variable Cox proportional hazards model were considered as significantly associated with the dependent variable.

4. ETHICAL CONSIDERATIONS

Ethical clearance was obtained from Institutional Review Board of Institute of Public Health, CMHS, and University of Gondar. After that support letter from Amhara Regional State Health Bureau for Felege Hiwot and DebreTabor hospitals was written and permission letter were also obtained from the hospitals administration and the ART focal persons in the three hospitals. Names and unique ART numbers of patients were not being included during data collection.

Moreover data collectors and supervisors were professionals who have experience of working in ART clinics.

5. RESULTS

5.1 Baseline socio-demographic characteristics of the study subjects

Out of 356 participants, 198(55.62 were males, the mean age of the patients was 36.13 ± 8.9 years, 167(46.91%) of the participants were in the age range between 30 to 39 years and 260 (73.03%) were urban dwellers (Table 1).

Table 1:- Baseline socio-demographic characteristics of HIV positive adults on second line ART at University of Gondar, Flege Hiwot referral and Debretabor Hospitals, September 1st, 2006 – April 8th, 2015.

Variable		Frequency	Percent (%)
Age	15-29	78	21.91
	30-39	167	46.91
	40-49	82	23.03
	>50	29	8.15
	Total	356	100.00
Sex	Male	198	55.62
	Female	158	44.38
	Total	356	100.0
Marital status	Unmarried	154	43.26
	Married	157	44.10
	Not recorded	45	12.64
	Total	356	100.00
Residence	Urban	260	73.03
	Rural	76	21.35
	Not recorded	20	5.62
	Total	549	100.0
Religion	Orthodox	297	83.43
	Muslim	15	4.21
	Protestant	6	1.69
	Not recorded	38	10.67
	Total	356	100.00
Educational status			
	No education	75	21.07
	Primary	75	21.07
	Secondary	105	29.49
	Tertiary	54	15.17
	Not recorded	47	13.2
	Total	356	100.00

5.2 Baseline clinical and immunological status of the study subjects

At start of first line ART, most of the patients, 326 (91.57%) were eligible for ART because of their WHO clinical staging and out of them 176(49.44%) were eligibly by both clinical and immunological (CD4 count) criteria. At the beginning of first line treatment 306(86%) start ART at advanced stage of the disease i.e. WHO clinical stage III and IV Regarding the functional status at first line ART start, majority 237(66.57%) were working and more than half of the study participants 213(59.8%), were having absolute CD4 count below 100 cells/milliliter.

Nearly half 162(45.51%) of the study subjects start first line ART with NRTI backbone of AZT based regimen followed by D4T, 133(37.36 %) and TDF, 61(17.13) and also NVP was NNRTI drub being taken by majority 257(72.2%) of the study subjects.
For 118(33.15%) of participants, first drug regimen was substituted and the majority 102(86.44%) modified only once and drug side effect was the reason for most of the regimen modification 82(70.7%) followed by TB 24 (20.7%).
The median time of stay on first line regimen was 42.56 months with an IQR of 37.78 months. Around 121(34%) of participants had previous history of TB treatment before switch to secondline ART. Up on switch to secondline ART, 210(59%) participants had recorded viral load and out of them 177(84.3%) had virological failure. Majority of the participants 331(93%) had also immunological failure at switch(Fig 2).

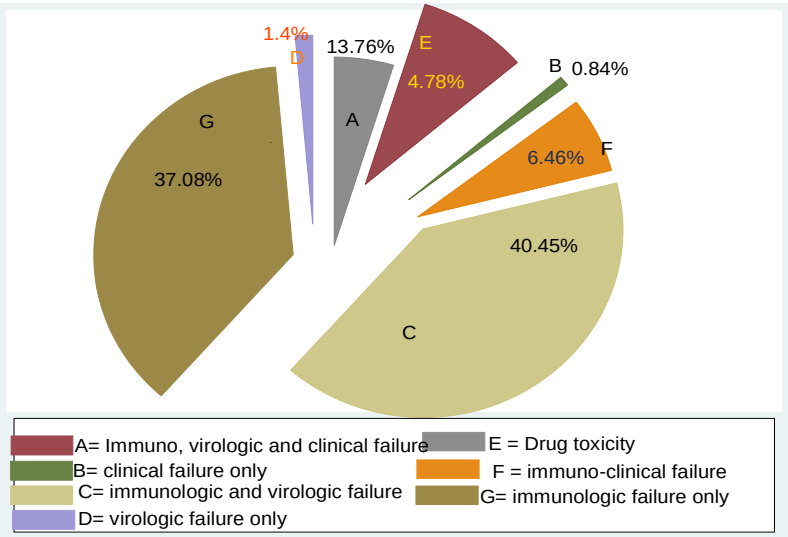

Figure2. Reasons of switch to secondline ART, at University of Gondar, Flege Hiwot referral and Debretabor Hospitals, September 1st, 2006 – April 8th, 2015.

At switch to second-line ART, majority of the patients were on WHO clinical stage III. The mean weight of participants at baseline were 52.45±10.84, more than half 206(57.87%) of the patients were taking TDF based secondline regimen and majority 289(81.18%) were taking ritonavir boosted lopinavir (Table 2).

Table 2:- Baseline and follow up clinical and immunological characteristics at switch of HIV positive adults on second line ART at University of Gondar, Felege Hiwot referral and Debretabor Hospitals, September 1st, 2006 – April 8th, 2015.

Variable	Category	Frequency	Percent (%)
WHO clinical stage	T stage I/II	127	35.67
	T stage III	172	48.31
	T stage IV	57	16.01
	Total	356	100.00
Functional Status at second line ART start	Working	298	83.71
	Ambulatory	35	9.83
	Bedridden	23	6.46
	Total	356	100.00
Number of Changed NRTI	None	19	5.31
	One	217	60.96
	Two	120	33.71
	Total	356	100.00
Protease inhibitor	LPV/r	289	81.18
	ATV/r	64	17.98
	NFV	3	0.84
	Total	356	100.00
NRTI backbone	TDF	206	57.87
	ABC	102	28.65
	AZT	41	11.52
	Others(d4t, ddi)	7	1.97
	Total	356	100.00
CD4 Count at switch	<100 cells/mm^3	122	62.36
	>=100 cells/mm^3	134	37.64
	Total	356	100.00
CPT	Yes	306	85.96
	No	50	14.04
	Total	356	100.00
INH Prophylaxis	Yes	33	9.27
	No	323	90.73
	Total	356	100.00

During the follow up period 24(6.74%) participants developed OI's other than those which classified in the clinical failure category. Some 18(5.06%) of the partcipants had also modified their second line treatment mainly due to drug out of stock12(66.67%). Recorded drug adverse effect were present in 23 (6.46%) of the partcicpants.

5.3 outcome of secondline ART Treatment

Study subjects were followed for a minimum of 6 months and a maximum of 104.467 months after switched to secondline ART and the median follow up period was 32.25 months (IQR=37.8 months).

A total of 67(18.82%) patients developed treatment failure and among them 24(35.82%) were immunological failure, 11(16.41%) clinical failure, 21(31.34%) death, and 11(16.41%) were lost to follow up. The remaining outcomes such as: transfer out and remaining on active follow up were, 24(6.74%), and 265(74.44%) respectively. Regarding the time of failure, 19 (28.3%) and 42(62.69%) of failures were reported within the first and second years of follow up respectively and the remaining 25(37.3%) of failures were recorded after third year of follow up. Study subjects were followed for different period of observation and total person time of observation was 1085.111 person-years (13021.33 person-months). There were a total of 67 failures and this makes the risk of failure after switch to secondline ART 67/1085.11 = 61.74 treatment failures per 1000 person years of observation. As well when we see it separately, for immunological failure, 24/1085.11=22.1 per 1000 person years , for clinical failure 11/1085.11 =10/1000 person year, for the 21 deaths, and the risk of death becomes 19 deaths/1000 person years and also the risk of lost to follow up becomes 11/1085.11 = 10/1000 person year.

As discussed earlier, for estimation of survival probability; treatment failure, death and lost to follow up were used as a composite outcome and were considered as failure and the model was fitted by using three of the outcomes as an event with a total of 67 observed events. The cumulative probabilities of survival at 12, 24, 60, and 96 months after switched to secondline ART were 0.94, 0.86, 0.7654, and 0.5772.

The overall median CD4 count was 79 with IQR of 118, for treatment failure was 67 cells/mm^3 with an IQR of 91 and 82 cells/mm^3 with an IQR of 122 for those who became censored at the end of the study.

Table 3: Outcome status of study subjects at the end of follow up with respect to their baseline socio-demographic and clinical characteristics of HIV positive adults on second line ART at University of Gondar, Felege Hiwot referral and Debretabor Hospitals, September 1st, 2006 – April 8th, 2015.

Variable	Outcomes at the end of follow up (Number (%))						Total
	Alive	Dead	LTFU	Immunological failure	Clinical failure	Transfer out	
Age							
15-29	56(21.13)	7(33.33)	2(18.2)	4(16.67)	4(36.36)	5(20.8)	78(21.9)
30-39	131(49.43)	10(47.62)	4(36.3)	7(29.17)	5(45.45)	10(41.7)	167(46.9)
40-49	62(23.4)	2(9.52)	2(18.2)	9(37.5)	1(9.09)	6(25)	82(23)
>=50	16(6.04)	2(9.52)	3 (27.3)	4(16.67)	1(9.09)	3(12.5)	29(8.2)
Sex							
Male	148(55.8)	10(47.6)	6(54.5)	15(62.5)	3(27.27)	16(66.7)	198(55.6)
Female	117(44.2)	11(52.4)	5(45.5)	9(37.5)	8(44.38)	8(33.3)	158(44.4)
Functional status at switch							
working	227(85.6%)	16(76.2)	7(636)	19(79.2)	9(81.82)	20(83.3)	298(83.7)
Ambulatory	27 (10.2)	0(00.00)	3(27.3)	3(12.5)	1(9.09)	76(4.2)	35(9.8)
Bedridden	11(4.2)	5(23.81)	1(9.1)	2(8.3)	1(9.09)	3(12.5)	23(6.5)
CPT							
On CPT	224(8.5)	18(85.7)	9(81.8)	22(91.7)	10(90.9)	23(95.8)	306(86)
Not on CPT	41(15.5)	3(14.3)	2(18.2)	2(8.3)	1(9.1)	1(4.2)	50(14)
WHO staging							
I or II	97(36.6)	4(19.0)	3(27.3)	8(33.3)	5(45.45)	10(4.7)	127(35.7)
III	133(50.2)	11(52.4)	4(36.4)	10(41.7)	4(36.36)	10(4.7)	172(48.3)
IV	35(13.2)	6(28.6)	4(36.4)	6(25)	2(18.18)	4(16.6)	57(16.0)
CD4 count as switch							
<100	159(60)	16(66.67)	8(72.7)	16(66.7)	6(54.55)	19(66.7)	222(62.4)
>=100	106(40)	8(33.3)	3(27.3)	8(33.3)	5(45.45)	8(33.3)	134(37.6)

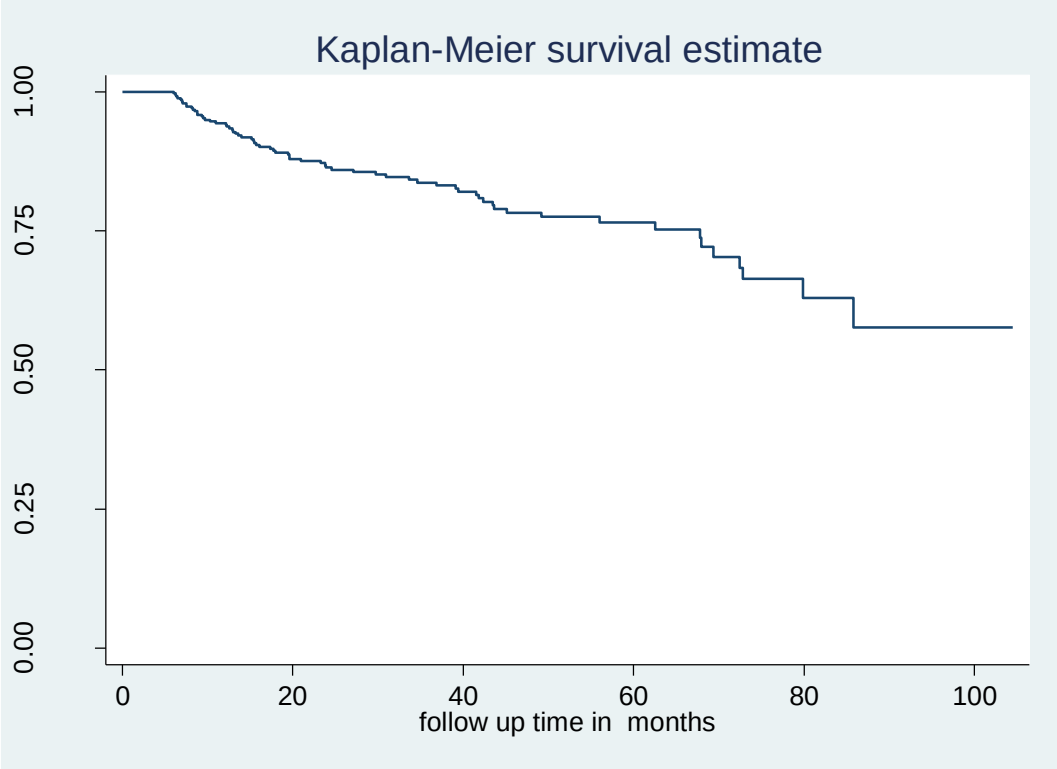

Fig 3:- Kaplan Meir survival curve of HIV positive adults on second line ART at University of Gondar, Felege Hiwot referral and Debretabor Hospitals, September 1st, 2006 – April 8th, 2015.

5.4 Predictors of secondline ART outcome

Log rank (Mantel-Henszel Cox) test of equality of survival for the different categories of explanatory variables: age, presence of immunological failure at switch, and CD4 were significantly associated with treatment failure.

Among median follow up period for those who have CD4 count<100 was 17 months with an IQR of 32.4 months where as for those whose CD4 count>=100 was 37.03 months with an IQR of 43.7 months. At the end of 24 and 60 months the survival of those whose CD4 count<100 was 83.86& and 72, 3 % respectively (Figure 3).

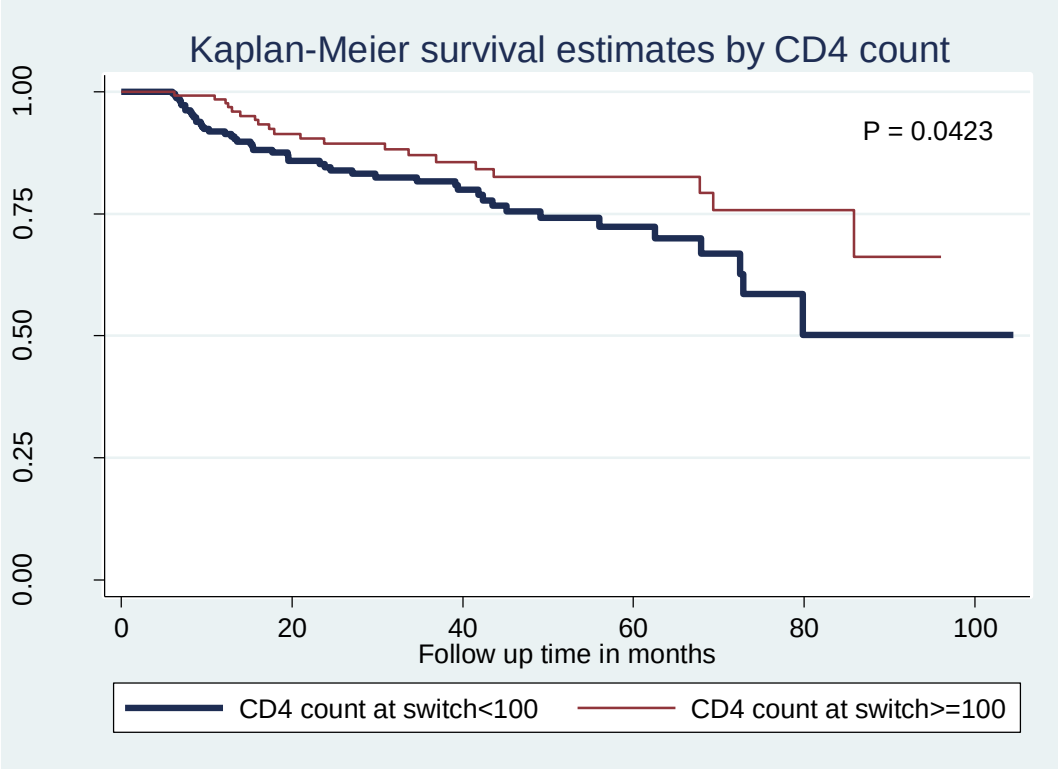

Fig 4:- Kaplan Meir survival curve by CD4 count at switch of HIV positive adults on second line ART at University of Gondar, Felege Hiwot referral and Debretabor Hospitals, September 1st, 2006 – April 8th, 2015.

Cox regression analysis

As can be noted from the findings of bi-variable Cox regression analysis, switching in the calendar year September 2013 to October 2014, change in weight, CD4 count <100cells/mm3(change in cd4 count), and being in WHO clinical stage IV were predictors treatment failure.

Consequently, in the multivariate Cox regression, to controls the undesirable effects of confounding variables, all variables which had p value less than 0.2 in the bi-variable analysis were included and a total of nine variables fitted in the model. Switching in the calendar year September 2013 to October 2014, change in weight(decrease in body weight), CD4 count <100cells/mm^3 at switch, being in WHO clinical stage IV at base line, and age category 50 years and above were independent predictors of treatment failure (the composite outcomes). But sex, INH prophylaxis, NRTI back bone at first line ART start and type of protease inhibitor being used at switch were not statistically significant.

Accordingly, being in WHO stage IV was 2.58 times higher risk than being in stageI/II (AHR = 2.58, 95% CI: 1.3, 5.14). Those individuals who have weight increment at the end of follow up as compared to the base line has a good outcome and for a unit increase in weight in kilogram the risk of developing the outcome decreased by 8.4% (AHR= 0.916,95%CI:0.88, 0 .955). Individuals in the age range 50 and above were 2.32 times at high risk than those individuals in the age group between 15 to 29 (AHR= 2.32, 95%CI: 1.0166, 5.32). Having CD4 count <100 cells/mm^3 at baseline increases the risk of developing the outcome 1.78 times as compared to those who have CD4 cont 100 and more(AHR=1.78, 95%CI:1.031, 3.07). Calender year of switch has also a significant effect and those who stated ART by 2013/20144 were 5.178 times at higher risk as compared to those who switched by 2008 and before(AHR= 5.178, 95%CI:1.162 23.076)(Tabl4).

Table 4:- Multivariate Cox regression analysis of predictors of secondline ART outcome of adult HIV positive University of Gondar, at Felege Hiwot referral and Debretabor hospitals, September 1st, 2006 – April 8th, 2015

Variable	Survival status		Crude HR (95% CI)	Adjusted HR (95% CI)
	Event	censored		
Age				
15-29	17	61	1	1
30-39	26	141	0.69(0 .376, 1.28)	0 .75(0.398, 1.4)
40-49	14	68	0.764(0.376,1.5)	0.81(0.39,1.68)
>=50	10	19	1.84(0.84, 4.024)	**2.326(1.016,5.324)**
Sex				
Male	34	164	0.84(0.52,1.37)	*
Female	33	125	1	
INH Prophylaxis				
Yes	3	30	2.27(0.712,7.22)	*
No	64	259	1	
WHO clinical T staging at switch				
I/II	20	107	1	
III	29	143	0.845(0.47,1.49)	0.96(0 .52, 1.745)
IV	18	39	1.59(0.83, 3.04)	**2.58(1.297, 5.14)**
Calendar year at switch				
Sept 2006 to Aug 2008	6	18	1	**1**
Sept 2008 to Aug 2011	37	105	2.07(0.78,5.5)	2.06(0.719,5.915)
Sept 2011 to Aug 2013	14	104	1.53(0.51,4.57)	1.324(0.393,4.463)
Sept 2013 to Oct 2014	10	62	4.45(1.43, 13.8)	**5.178(1.162,23.076)**
CD4 cell count				
<100 cells/mm^3	47	175	1.76(1.01,2.9)	**1.78(1.03, 3.077)**
>=100cells/mm^3	20	114	1	
NRTI at first line ART start				
D4T	29	104	1	
AZT	15	137	0.86(0 .5,1.47)	*****
TDF	13	48	1.8(0.916, 3.56)	*

* Non significant from the multivariate Cox regression

6. DISCUSSION

As defined by the composite outcome, immunological failure, clinical failure, death and lost are considered as treatment failure. According to this study treatment failure was 67/356(18.8% (95%CI: 14.74%, 22.9%). When we see each of the outcomes separately, at the end of the follow up, 24(6.74 %(95%CI: 4.1%,9.36%)) developed immunological failure, 11(3.09%(95%CI: 1.28%, 4.9%)) developed clinical failure, 21(5.9% 95%CI:3.44%, 8.36%)) died, 11(3.09%(95%CI: CI:1.28%, 4.9%)) lost to follow up, 24(6.74 %(95%CI: 4.1%,9.36%)) transferred out to another facility and the remaining 265(74.44%(95%CI: 69.8%, 79%) were alive.

In our case, treatment failure was18.8% (95%CI: 14.74%, 22.9%) which is consistent with multi-centered study conducted in Asia and Africa having 19% failure at the end of follow up and with also a meta analysis having a range of outcomes (28). But it is lower than a retrospective follow up study done in rural South Africa among patients switched due to virological failure from first line treatment having treatment failure of 25.1%, (26) and in the same setting with another study having treatment failure at 24 month of 25% unlike ours which was 11.8% at 24 months(27) and it is also lower than another observational cohort study done in South Africa having the rate of failure of 13% by the end of 12 month after switch while ours was 5.34% at the end of 12 month of follow up(29).Even if the variation is minimal, it might be occur due to difference in approach in which, they were included patients who switched due to virological failure at unlike ours in which patients switched by different reasons. These patients who switched by virological failure might be debilitated at the start of secondline ART and that might affect their outcome. The other reason is that as different studies showed patients who had higher viral load at switch are at higher risk of viral mutation and drug resistance, and they will end up with failure.

But our finding is higher than the studies done in six sub Saharan Africa countries in which they assessed by different approaches and according to their result(13.9%) experienced virological failure, 12.1% of patients developed immunological failure and 6.3 percent experienced clinical failure(25), a study conducted in Nigeria by virological

monitoring having treatment failure of 10% at the end of the study(30). The difference might be explained by difference of classification since in our case we considered those immunologically, clinically failed, dead and lost as a failure. Furthermore, variation in setting and scope of the studies has also non-negligible effect.

Regarding the incidence of failure, we found that 61.74 (95%CI: 48.6, 78.45) failures per 1000 person year and it is consistent with a study done in Asia among those who used secondline ART in which the incident rates of treatment failure was 88 (95% CI: 71 to 109)per 1000 patient/years (23). But it is lower than a to multi-centered study conducted in Asia and Africa, with an overall Incidence of 195 per 1000 person-years e(24) and which might be due to the occurrence of higher failure in the early phase of switch and the difference might because of having longer follow up in our case.
Transfer out to another setting was 6.74 %(95%CI: 4.1%,9.36%) and it is similar with a study done in rural south Africa to 7.9% south Africa 4.57 % (26) (34)but it is lower than another study done in sub Saharan countries having TO of 1.6% (25) which can be explained by to shorter period of follow up they had in which many patients might not leave the facilities. Retention in care in our case was 74.44 %(95%CI: 69.8%, 79%) and it is similar with studies done in different sub-Saharan African countries (25, 26).

Being in the WHO clinical stage IV increases the risk of treatment failure 2.58(95% CI: 1.297, 5.144) as compared to those in stage I&II at switch and also it increases the risk of failure 2.7(95%CI: 1.4, 5.2) as compared to being in stage III. This finding is consistent with studies in Malawi and in Sub-Saharan Africa (46). This might be due to the fact that those patients who had advanced disease are at higher risk of drug resistance, viral mutation and having an advanced opportunistic disease which further compromises their immunity and that might compromise their response to treatment after switch.
Having lower CD4 count (<100) is also the other predictor of failure which increases the rate of failure by 1.78(95%CI: 1.03, 3.077). This is consistent with studies done in Thailand, Malawi, and South Africa (24, 29, 46). This might be due to patients who had very low CD4 count are labile to have different opportunistic diseases and the added

burden of these diseases further complicate their response and they might end up with failure and/or death.
Those participants in the age category of 50 or more are 2.87(95%CI: 1.224, 6.747) times, 3.11(955CI: 1.44, 6.7) and 2.3263 (95%CI: 1.0166, 5.32) times at higher risk of failure than those in the age group between 40 to 49, 30 to 39 and 15 to 29 respectively. This is consistent with a study done in Asia(23). This can be explained by decreasing of immunity in the elderly, vulnerability to chronic co-morbidities and also those patients in this age group were those who took medications for longer period of time and it might be associated with drug resistance and poor adherence caused by longer in take.

A positive change in weight at the end of follow up as compared to baseline was a significant predictor of failure and for a unit increment of body weight in kilo gram, the risk of failure will decrease by 8.4%(AHR=0.95%CI:0.88,0.955).This might be consistent with studies which considered BMI (46). This might be explained by the consideration of weight gain as an indicator of good response to treatment.

Those patients who switched in the calendar year September 2013 until October 2014 were also 5.18(95%CI: 1.16, 23.076) times at higher risk of failure than those who switched before September 2008. This also can be explained by the fact that majority of those who switched recently are patients who were taking ART medication for longer period of time and that can cause viral mutation and drug resistance. More over this clients might be delayed on failing first line regimen and that might compromise their response after switch.

7. LIMITATIONS AND STRENGTHS

The big limitations of this study is that data is collected from secondary source, it suffers from data incompleteness especially for follow up values which the study faces difficulty to see clinical and immunological responses of patients.

Especially missing of some patient cards might cause survivor bias due to the hospitals dispose cards which are not actively being used by patients, and this might under estimate our outcome.

Considering treatment failure as a composite outcome of immunological failure, clinical failure, dead and lost might inflate our finding.

Strength of the study: the study was conducted in three big hospitals which increase its representativeness and also the longer duration of follow up period is good to have adequate number of events.

8. CONCLUSIONS

- Treatment failure was comparable as compared to many sub-Saharan studies.
- Most of the failures occurred during the first two years after switch and decreased after the third year of switch.
- Being in WHO clinical stage IV, CD4 count<100, change in weight, Age category 50 or more and switching in the calendar year 2014 were found to be predictors of treatment failure and an alternative third line ART should be considered for those who are on failing regimen.

9. RECOMMENDATIONS

1. **To health care providers managing HIV patients**
   - Careful follow up and monitoring of patients on secondline ART need to be strengthened
   - To focus on regular nutritional assessment and support of patients
   - Especial care and support should be given for the elderly ART users.
2. **To governmental and nongovernmental organizations**
   - To strengthen careful follow up and regular viral load monitoring of patients on secondline ART
   - To find a possible way to start third line alternative for failing patients.
3. **To researchers**
   - Prospective follow up study with virological monitoring is strongly recommended to come up with a strong evidence

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11. Annexes

Data collection Check list

This checklist is prepared for the collection of socio-demographic, clinical, immunological, treatment and outcome related information that are important for the assessment of outcome and predictors of second line antiretroviral therapy in University of Gondar Hospital, Felege Hiwot referral Hospital and Debre Tabor Hospital. All this information will be retrieved from the clients ART and pre-ART registration book and from individual patient card without mentioning the name of clients. This information will be collected by health care providers (BSc nurse or Health Officer) possibly working in the ART clinic of the hospitals. **Contact Information** ***Adino Tesfahun Tel +251-918-068614 Mr. Tadesse Awoke Tel: +251-910-173308 Dr. Mamo Wubshet Tel:+251-912-180307***

Part I: Baseline variables

S.No	**Variables**	**Categories**
101.	Hospital/Facility	
102.	Patient_MRN number	
103.	Age at enrollment	____years
104.	Date of enrollment	--------/------/----------(dd/mm/yy)
105.	Gender	1 Female 2 Male
106.	Address	Zone_____ Woreda_____ Kebele_____
107.	Marital status	1. Single 2. Married 3.Divorced 4. Widowed 5. Separated
108.	Education	1.No education 2.Elementary 3 .Secondary 4 .Tertiary
109.	Occupation	1.Unemployed 2.Government 3.Non government 4. Private 5 .Other
110.	Religion	1. Orthodox 2. Muslim 3. Protestant 4. Catholic 5. Others
111.	Care giver relation	1 Father/Mother 2 Son/daughter 3 brother/sister 4 other relative 5 Spouse 6. No care giver
112.	Pastopportunistic infections at enrollment	1 Yes 2. No If yes, Specify(list all) _____
113.	TB treatment history at enrollment	1. Yes 2. No 3. Not recorded **If yes date ----------** **Treatment outcome----------**
114.	Number of house hold	_____persons
115.	Disclosure status	1. Spouse 2. Relatives 3. Child (ren) 4. Parents 5. Siblings 6. Other 7.No
116.	Substance use	1 Tobacco 2. Alcohol 3. Khat 4. None
117.	First line ART start date	------/----------/----------(dd/mm/yyyy)
118.	Baseline Weight	_____kgm

119.	Baseline Height	_____cm						
120.	Baseline CD4 count	_____						
121.	Baseline WHO stage	1 Stage I	2. Stage II	3. Stage III	4. Stage IV			
122.	Baseline Functional status	1 Working	2. Ambulatory	3. Bedridden				
123.	Reasons of eligibility for ART	1. Clinical 2. CD4 count	3. Viral load 4. TLC	5. Transfer in 6. Other				
124.	Original regimen	1. 1a(30) 2. 1a(40)	3. 1b (30) 4. 1b(40	5. 1c 6. 1d	7. 1e 8. 1f	9. 1g 10. 1h	11.1i 12. 1j	
125.	Was the Regimen modified before switch to second line changed?	1. Yes	2. No		If No to			
126.	How many times was it modified?	1. Once	2. Two times	3. Three times				
127.	When was it modified?	1st------/-------/----------(DD/MM/YY)		2nd------/--------/----------(DD/MM/YY)		3rd-------/-------/----------(DD/MM/YY)		
128.	New regimen	1. 1st _____	2. 2nd_____	3. 3rd_____				
129.	Reason for modification	1st	1. Side effects	2. TB	3. Pregnancy	4. Others		
		2nd	1. Side effects	2. TB	3. Pregnancy	4. Others		
		3rd	1. Side effects	2. TB	3. Pregnancy	4. Others		
130.	Opportunistic infections during first line treatment	OI---------- Date ---------- OI---------- Date---------- OI---------- Date---------- OI---------- Date----------			OI---------- Date OI---------- Date---------- OI---------- Date----------			
131.	TB treatment history during first line treatment	2. Yes	2. No	3. Not recorded	**If yes date** ---------- **Treatment outcome**----------			
132.	Date the regimen changed to second line	-----/-----/-------- (DD/MM/YY)						
133.	Reason for switch	1. Clinical failure	2. Immunologic failure	3. Virologic failure	4. Drug toxicity	Other(specify		
134.	Viral load at switch							

Part III: Follow-up variables after switch to second line ART

Date	Weight	F. Status	WHO stage	TB screen (P/N/on Rx)	OIs	INH	CPT /Adhe(G, F,P)	ARV drug					Hgb	CD4 count	Last Status				
								Adherence	**Code of regimen**	Regimen change (Y/N)	R. for change	Side effect			Alive	Tx.failur	Dead	Lost to follow	Transfer out

1. **stage IV defining OI----------Date----------
2. **stage IV defining OI----------Date----------
3. **stage IV defining OI----------Date----------
4. **stage IV defining OI----------Date----------

Collected by: Name _____ Signature _____Date _____

Supervised by: Name _____ Signature _____ Date _____

Annex 2 . ART regimens

Declaration

I, the undersigned, senior MPH student declare that this thesis proposal is my original work in partial fulfilment of the requirement for the degree of Master of Public Health in Epidemiology and Biostatistics.

Name: Adino Tesfahun
Signature: _____

Place of submission: Institute of public Health, College of Medicine and Health Sciences, University of Gondar.

Date of Submission: _____

This thesis proposal has been submitted for ethical evaluation with our approval as university advisor(s).

Advisors

Name	Signature
1. Dr. Mamo Wubshet	----------
2. Ato Tadesse Awoke	----------

ASSURANCE OF INVESTIGATOR

I, the undersigned, senior MPH student agree to accept responsibility for the scientific, ethical and technical conduct of the research project and for provision of required progress reports as pre terms and conditions of the research and publications office of the University of Gondar.

Name of the student: Adino Tesfahun

Date: _____ Signature: _____

Approval of the advisor (s)

Advisors

	Name	Signature	Date
1.	Dr. Mamo Wubshet	_____	_____
2.	Ato Tadesse Awoke	_____	_____